

Mesenchymal-Specific Inhibition of Vascular Endothelial Growth Factor (VEGF) Attenuates Growth in Neonatal Mice.

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Public Summary:

Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis and vasculogenesis. However, the role of VEGF in the regulation of neonatal mouse development is not completely defined. We sought to determine the effect of VEGF inhibition on the development of the neonatal mouse using a transgenic approach. **MATERIALS AND METHODS:** We generated triple transgenic mice that express the soluble VEGF receptor, (sFlt-1), specifically in the mesenchyme (dermo-1(Cre)- tetracycline reverse transcriptional activator (rtTA)(flox/flox)-tet(0)-sflt-1). Mothers of the pups (transgenic and littermate controls) were fed doxycycline chow at birth for transgene activation via breast milk, and the pups were sacrificed at various time points. To test reversibility of the phenotype, mice from both groups (n = 6) were switched to normal chow at P50 and monthly weights were measured for 9 mo. **RESULTS:** Dermo-1(Cre)-rtTA(flox/flox)-tet(0)-sflt-1 mice were smaller compared with littermate controls at P21. There was a significant reduction in tissue VEGF levels following sFlt-1 expression. The rate of growth was reduced but did not impact overall survival after 1 y. A significant reduction in organ size as a percentage body weight was seen in the kidney and stomach, whereas the weight of the colon and spleen were relatively increased; however, no gross histologic difference was observed. After 6 mo on normal diet, the dermo-1(Cre)-rtTA(flox/flox)-tet(0)-sflt-1 mouse's weight doubled, indicating reversibility of phenotype. **CONCLUSION:** Mesenchymal-specific inhibition of VEGF in neonatal mice results in a severe but reversible arrest in somatic growth that does not affect overall survival at 1 yr. This mouse is a useful tool to test the function of VEGF in somatic growth.

Scientific Abstract:

BACKGROUND: Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis and vasculogenesis. However, the role of VEGF in the regulation of neonatal mouse development is not completely defined. We sought to determine the effect of VEGF inhibition on the development of the neonatal mouse using a transgenic approach. **MATERIALS AND METHODS:** We generated triple transgenic mice that express the soluble VEGF receptor, (sFlt-1), specifically in the mesenchyme (dermo-1(Cre)- tetracycline reverse transcriptional activator (rtTA)(flox/flox)-tet(0)-sflt-1). Mothers of the pups (transgenic and littermate controls) were fed doxycycline chow at birth for transgene activation via breast milk, and the pups were sacrificed at various time points. To test reversibility of the phenotype, mice from both groups (n = 6) were switched to normal chow at P50 and monthly weights were measured for 9 mo. **RESULTS:** Dermo-1(Cre)-rtTA(flox/flox)-tet(0)-sflt-1 mice were smaller compared with littermate controls at P21. There was a significant reduction in tissue VEGF levels following sFlt-1 expression. The rate of growth was reduced but did not impact overall survival after 1 y. A significant reduction in organ size as a percentage body weight was seen in the kidney and stomach, whereas the weight of the colon and spleen were relatively increased; however, no gross histologic difference was observed. After 6 mo on normal diet, the dermo-1(Cre)-rtTA(flox/flox)-tet(0)-sflt-1 mouse's weight doubled, indicating reversibility of phenotype. **CONCLUSION:** Mesenchymal-specific inhibition of VEGF in neonatal mice results in a severe but reversible arrest in somatic growth that does not affect overall survival at 1 yr. This mouse is a useful tool to test the function of VEGF in somatic growth.